Copy for the Elected Office (EO/US)

PCT/GB00/03729

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

WRIGHT Robert Gordon McRae
Elkington and Fife
Beacon House
113 Kingsway
London WC2B 6PN
ROYAUME-UNI

Date of mailing (day/month/year)
13 February 2002 (13.02.02)

Applicant's or agent's file reference
P202119WO

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/03729

International filing date (day/month/year)
29 September 2000 (29.09.00)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address
BROWNE, Robin, Forsythe
Urquhart-Dykes & Lord
Tower House
Merrion Way
Leeds LS2 8PA
United Kingdom

State of Nationality:
State of Residence:
Telephone No.: 0113 245 2388
Facsimile No.: 0113 242 0446
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
WRIGHT Robert Gordon McRae
Elkington and Fife
Beacon House
113 Kingsway
London WC2B 6PN
United Kingdom

State of Nationality:
State of Residence:
Telephone No.: +44 (0) 1732 458881
Facsimile No.: +44 (0) 1732 450348
Teleprinter No.:

3. Further observations, if necessary:
The power of attorney signed by all applicant will be required.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Ki-Nam HA
Telephone No.: (41-22) 338.83.38

004657846

Form PCT/IB/306 (March 1994)

PATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
P202119WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/ 03729	29/09/2000	01/10/1999
Applicant		
NORTON HEALTHCARE LTD		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

[ ] None of the figures.

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No
GB 00/03729

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20 A61K9/16 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 01368 A (NORTON HEALTHCARE LTD ;WOOLFE AUSTIN JOHN (GB)) 13 January 2000 (2000-01-13) page 3 page 5; example 1 ---	1-5, 8-11,14, 15
P,X	WO 00 15200 A (NORTON HEALTHCARE LTD ;WOOLFE AUSTEN JOHN (GB)) 23 March 2000 (2000-03-23) page 2, line 3 -page 3, line 27 ---	1-13
P,X	WO 00 56339 A (PHARMASCIENCE INC ;OUALI AOMAR (CA); AZAD ABUL KALAM (CA)) 28 September 2000 (2000-09-28) claims --- -/--	1-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 February 2001	06/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040. Tx. 31 651 epo nl. Fax: (+31–70) 340–3016	Boulois, D

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP 1 020 182 A (SHERMAN BERNARD CHARLES) 19 July 2000 (2000-07-19) page 3 -page 4; examples 1-4	1,4,5, 7-11,14, 15
E	EP 1 068 867 A (SHERMAN BERNARD CHARLES) 17 January 2001 (2001-01-17) page 3 -page 4; example 1	1-5, 7-11,14, 15
X	WO 91 16895 A (SEARLE & CO) 14 November 1991 (1991-11-14) cited in the application page 5, line 4 - line 20	1,4,5, 7-12,14, 15
A	WO 91 16886 A (SEARLE & CO) 14 November 1991 (1991-11-14) cited in the application page 4, last paragraph -page 5, paragraph 1	1
A	US 5 232 704 A (FRANZ MICHEL R ET AL) 3 August 1993 (1993-08-03) column 18 -column 19; example 1	1

1

INTERNATIONAL SEARCH REPORT

[redacted]ation on patent family members

[redacted]ternational Application No
[redacted]/GB 00/03729

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0001368 A	13-01-2000	AU 4519399 A	24-01-2000
WO 0015200 A	23-03-2000	AU 5750799 A	03-04-2000
WO 0056339 A	28-09-2000	AU 3269200 A	09-10-2000
EP 1020182 A	19-07-2000	NONE	
EP 1068867 A	17-01-2001	AU 4719200 A	18-01-2001
WO 9116895 A	14-11-1991	AT 121625 T	15-05-1995
		AU 7876491 A	27-11-1991
		CA 2082944 A,C	04-11-1991
		DE 69109286 D	01-06-1995
		DE 69109286 T	28-09-1995
		DK 527887 T	03-07-1995
		EP 0527887 A	24-02-1993
		ES 2071312 T	16-06-1995
		GR 3015939 T	31-07-1995
		IE 911486 A	06-11-1991
		IL 98033 A	31-07-1995
		NZ 238024 A	26-08-1993
		PT 97562 A,B	28-02-1992
		US 5601843 A	11-02-1997
		US 5698225 A	16-12-1997
		ZA 9103353 A	28-04-1993
WO 9116886 A	14-11-1991	AU 8089091 A	27-11-1991
		IE 911485 A,B	06-11-1991
		IL 98034 A	31-10-1996
		NZ 238023 A	26-08-1992
		PT 97550 A,B	28-02-1992
		US 5213807 A	25-05-1993
		ZA 9103354 A	29-07-1992
US 5232704 A	03-08-1993	NONE	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/03729

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20 A61K9/16 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 01368 A (NORTON HEALTHCARE LTD ;WOOLFE AUSTIN JOHN (GB)) 13 January 2000 (2000-01-13) page 3 page 5; example 1 ---	1-5, 8-11,14, 15
P,X	WO 00 15200 A (NORTON HEALTHCARE LTD ;WOOLFE AUSTEN JOHN (GB)) 23 March 2000 (2000-03-23) page 2, line 3 -page 3, line 27 ---	1-13
P,X	WO 00 56339 A (PHARMASCIENCE INC ;OUALI AOMAR (CA); AZAD ABUL KALAM (CA)) 28 September 2000 (2000-09-28) claims --- -/--	1-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 February 2001	06/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Boulois, D

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/03729

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP 1 020 182 A (SHERMAN BERNARD CHARLES) 19 July 2000 (2000-07-19) page 3 -page 4; examples 1-4	1,4,5, 7-11,14, 15
E	EP 1 068 867 A (SHERMAN BERNARD CHARLES) 17 January 2001 (2001-01-17) page 3 -page 4; example 1	1-5, 7-11,14, 15
X	WO 91 16895 A (SEARLE & CO) 14 November 1991 (1991-11-14) cited in the application page 5, line 4 - line 20	1,4,5, 7-12,14, 15
A	WO 91 16886 A (SEARLE & CO) 14 November 1991 (1991-11-14) cited in the application page 4, last paragraph -page 5, paragraph 1	1
A	US 5 232 704 A (FRANZ MICHEL R ET AL) 3 August 1993 (1993-08-03) column 18 -column 19; example 1	1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

[redacted] al Application No
PCT/GB 00/03729

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0001368 A	13-01-2000	AU 4519399 A	24-01-2000
WO 0015200 A	23-03-2000	AU 5750799 A	03-04-2000
WO 0056339 A	28-09-2000	AU 3269200 A	09-10-2000
EP 1020182 A	19-07-2000	NONE	
EP 1068867 A	17-01-2001	AU 4719200 A	18-01-2001
WO 9116895 A	14-11-1991	AT 121625 T	15-05-1995
		AU 7876491 A	27-11-1991
		CA 2082944 A,C	04-11-1991
		DE 69109286 D	01-06-1995
		DE 69109286 T	28-09-1995
		DK 527887 T	03-07-1995
		EP 0527887 A	24-02-1993
		ES 2071312 T	16-06-1995
		GR 3015939 T	31-07-1995
		IE 911486 A	06-11-1991
		IL 98033 A	31-07-1995
		NZ 238024 A	26-08-1993
		PT 97562 A,B	28-02-1992
		US 5601843 A	11-02-1997
		US 5698225 A	16-12-1997
		ZA 9103353 A	28-04-1993
WO 9116886 A	14-11-1991	AU 8089091 A	27-11-1991
		IE 911485 A,B	06-11-1991
		IL 98034 A	31-10-1996
		NZ 238023 A	26-08-1992
		PT 97550 A,B	28-02-1992
		US 5213807 A	25-05-1993
		ZA 9103354 A	29-07-1992
US 5232704 A	03-08-1993	NONE	

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P202119WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/03729	29/09/2000	01/10/1999
International Patent Classification (IPC) or national classification and IPC A61K9/20		
Applicant NORTON HEALTHCARE LTD et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26/04/2001	05.02.2002
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Boulois, D Telephone No. +31 70 340 3878

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/03729

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-7 as originally filed

Claims, No.:

1-15 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,3,6,13
	No:	Claims	1,4,5,7-12,14,15
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Application No Patent No (day/month/year) (day/month/year) (day/month/year)	Publication date Filing date Priority date (valid claim)		
WO-A-0001368 (E1)	15/1/2000	30/6/1999	1/7/1998
WO-A-0015200 (E2)	25/3/2000	10/9/1999	10/9/1998
WO-A-0056339 (E3)	28/9/2000	20/3/2000	22/3/1999
EP-A-1020182 (E4)	19/7/2000	17/1/2000	8/1/1999
EP-A-1068867 (E5)	17/1/2001	13/7/2000	14/7/1999

The disclosure of the documents E1, E2, E3, E4 and E5 will be taken in consideration for the judgement of novelty of the following claims in the regional phase:

- lack of novelty of claims 1-5, 8-11,14 and 15 towards E1
- lack of novelty of claims 1-13 towards E2
- lack of novelty of claims 1-15 towards E3
- lack of novelty of claims 1,4,5,7-11,14,15 towards E4
- lack of novelty of claims 1-5, 7-11,15 towards E5

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 April 2001 (12.04.2001)

PCT

(10) International Publication Number
WO 01/24778 A1

(51) International Patent Classification[7]: A61K 9/20, 9/16, 9/50

(21) International Application Number: PCT/GB00/03729

(22) International Filing Date:
29 September 2000 (29.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

9923139.1	1 October 1999 (01.10.1999)	GB
0000483.8	11 January 2000 (11.01.2000)	GB

(71) Applicant *(for all designated States except US)*: **NORTON HEALTHCARE LTD.** [GB/GB]; Albert Basin, Royal Docks, London EC16 2QJ (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **WOOLFE, Austen, John** [GB/GB]; 31 Emberson Way, North Weald, Essex CM19 6DL (GB).

(74) Agent: **BROWNE, Robin, Forsythe**; Urquhart-Dykes & Lord, Tower House, Merrion Way, Leeds LS2 8PA (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/24778 A1

(54) Title: ANTI-INFLAMMATORY PHARMACEUTICAL FORMULATIONS

(57) Abstract: An oral pharmaceutical dosage form including a mixture of a delay release formulation of a non-steroidal anti-inflammatory drug (NSAID) and a mixture containing a prostaglandin and one or more excipients.

ANTI-INFLAMMATORY PHARMACEUTICAL FORMULATIONS

This invention relates to pharmaceutical formulations of anti-inflammatory drugs, particularly non-steroidal anti-inflammatory drugs (NSAIDs).

These NSAIDs are used for the treatment of inflammatory conditions such as osteoarthritis or rheumatoid arthritis. A side effect of the oral administration of NSAIDs particularly with long term usage, is a liability to ulcerogenic effects. NSAID induced ulcers in the stomach are potentially dangerous because few or no symptoms may be detected until significant damage has been caused. Certain prostaglandins, for example misoprostol have been shown to reduce and even prevent such ulcers.

Various patent applications relate to use of misoprostol with immediate release drugs, for example GB-A-2135881 (Farmitalia Carlo Erba), WO91/16896 (G D Searle), or where a gastric resistant coating is put over the NSAID in an attempt to reduce further gastric erosion due to release in the stomach of the NSAID, for example WO91/16895, WO91/16886 (G D Searle).

There is an increasing use of sustained release preparations of NSAID drugs to reduce the number of doses required by the patient each day. Although the theory of such preparations is that the majority of the drug is released in the intestine rather than the stomach, in practice there is a significant occurrence of gastric problems. This may be due to release of small amounts of drug within the stomach.

The incorporation of misoprostol into such products to reduce the potential for such problems has not previously been disclosed.

According to the present invention an oral pharmaceutical dosage form includes a mixture of a delay release formulation of a NSAID and a mixture containing one or more excipients and a prostaglandin, wherein the delay release NSAID formulation preferably comprises coated granules.

The prostaglandin mixture may be provided in the form of a powder which is mixed with the NSAID formulation within the dosage form.

The dosage form may comprise a tablet, capsule, granule or other commonly used configuration. However preferred dosage forms comprise a capsule containing multi-particulate granules of the NSAID formulation together with the powdered prostaglandin mixture. The NSAID granules preferably have coatings adapted to provide programmed release according to the position in the gastrointestinal tract. Use of such coated granules provides a more repeatable release along the gastrointestinal tract and may reduce gastric erosion because the small pellets or granules are easily moved and do not adhere readily to the folds of the gastric wall.

Granules for use in accordance with this invention may have a single slowly erodible coat or may comprise mixtures of granules with differing levels or types of coating adapted to provide a continuous or distributed release profile through the gastrointestinal tract. The delay afforded may range from a minimal delay to several hours, dependent on the pH of the gastrointestinal tract in the immediate vicinity.

The NSAID is preferably but not exclusively one of reasonably low weight per standard dose, that is 200 mg or below. Examples of suitable NSAIDs include tiaprofenic acid, piroxicam, flubiprofen, tenoxicam, meloxicam or similar molecules. Salts or other derivatives of these

drugs may be employed in a conventional manner. Most preferably the drug is diclofenac sodium, ketoprofen or indomethacin. Mixtures may be used.

Drug delivery using capsules avoids a further compression step as may be necessary during tablet manufacture.

Granules, for example composed of diclofenac sodium and a methyl methacrylate (eg Eudragit L 30 D-55) may be prepared by blending the ingredients in a planetary mixer with slow addition of water to produce granules. In a preferred process very fine granules are produced to avoid a need for milling before compaction into tablets or incorporation into capsules. Use of granules with the dimension of 200 - 1000 μm, preferably 300 to 500 μm is particularly suitable. Tablets may be produced by coating these granules with a barrier coating material for example a cellulosic material such as hydroxypropylmethyl cellulose or hydroxypropyl cellulose. Tablets may be produced by coating these granules.

An alternative method of forming coated granules is by spraying a solution of Eudragit onto a bed of diclofenac sodium or other drug and any necessary excipients for example using a fluid bed coating apparatus. The process is preferably controlled to produce fine granules which do not require milling before incorporation into tablets or capsules.

The coating for the granules may include cellulose derivatives eg hydroxypropyl methyl cellulose, methacrylic acid and derivatives eg methyl methacrylates for example, Eudragrit® (Rhom Pharm), especially Eudragrit L or S. Other standard enteric coating materials may be used for example phthalates, eg cellulose acetate phthalate or preferably hydroxypropylacetate phthalate or polyvinylacetate

phthalate. Mixtures of these and other materials may be used to produce delay release coated beads. Normally the coating will include plasticisers eg polyethylene glycol, triacetin or phthalate esters.

The prostaglandin component preferably contains misoprostol optionally together with one or more inert excipients. The prostaglandin is normally provided as a 1:10 or 1:100 dilution on an inert cellulose or other binder or filler. Especially useful material for this invention is hydroxypropyl methyl cellulose. The dosage of prostaglandin may be chosen to be suitable to prevent or reduce stomach ulceration caused by the NSAID. A suitable dose of misoprostol is between 10 - 50 μg preferably 50 - 200 μg per dosage form but this may be increased or decreased depending on the NSAID used.

Preferred dosage forms comprise capsules, preferably hard gelatin capsules.

Tablets where the prostaglandin is mixed with one or more binding agents may be bi-layer tablets wherein the NSAID is formed into a first layer and the prostaglandin is then compressed onto it. A tri-layer tablet with an inert intermediate barrier layer between the NSAID and prostaglandin layers may be employed.

In preferred embodiments of the invention, the potential for gastric erosion is reduced by ensuring that the prostaglandin is released before the NSAID. Any beads for immediate or rapid release are coated with an inert coating which defer solubility in gastric fluid, for example for a period of 30 minutes. Such materials include cellulose derivatives for example hydroxypropyl methyl cellulose, methyl or ethyl celluloses or other sealants eg Zein. Thin coatings of methacrylate derivatives eg polyhydroxymethacrylate or other materials such as hardened

gelatine, waxes, starches or polyvinyl pyrrolidone may be used. Other portions of the granules may be coated with methacrylate derivatives, phthalate, for example hydroxypropyl methyl cellulose phthalate or similar materials to give an appropriate release profile as is well known in the art.

The invention is further described by means of example, but not in any limitative sense.

Example 1

The following formulation was mixed with water in a planetary mixer to make enteric coated granules:

diclofenac sodium	96.2%
Eudragit L 30 D-55	3.8%

The granules were dried and compacted into layered tablets having the following composition:

diclofenac-containing granules	26.0%
microcrystalline cellulose	73.5%
magnesium stearate	0.5%

The tablets were compared to a proprietary diclofenac-containing tablet available under the trade mark Arthrotec. Bioequivalence studies showed the release of diclofenac to be essentially similar.

Granules containing 35% diclofenac sodium ie 75 mg drug per dose were prepared.

EXAMPLE 2

A two layer tablet was made as follows:

The following ingredients were mixed together:

Diclofenac sodium	75.95%
Eudragit l30-d55 (30% solid dispersion)	12.66%
Lactose (20 mesh)	11.4%
Water	

The mixture was blended, dried and milled to give diclofenac-containing granules. The granules (25%) were mixed with microcrystalline cellulose (Avicel pH 200 and pH 112) to give a total of 69%. Dry Eudragit l100 powder (5%) and hydrogenated castor oil (1%) were added. The mixture was pressed into half tablets with a tablet weight of 400 mg.

A misoprostol layer was formed as follows:

A misoprostol dispersion (1:100) 6.7% was combined with microcrystalline cellulose (Avicel pH 112) 88.33%, croscarmelose sodium (4%) and hydrogenated castor oil to give a tablet weight of 300 mg. The combined bi-layered tablet had a total weight of 700 mg.

Dissolution properties were determined by exposure to acid medium for two hours followed by measurement of dissolution in alkaline buffer. The following results were obtained.

SOLUBILITY/%		
Time in alkaline buffer	Example 2 tablets	Arthrotec tablets
30 sec	1.6 - 5.0	0 - 0.5
5 min	11 - 13	1.3 - 3.1
30 min	51 - 60	61 - 71
60 min	86 - 90	74 - 96

CLAIMS

1. An oral pharmaceutical dosage form including a mixture of a delay release formulation of a non-steroidal anti-inflammatory drug (NSAID) and a mixture containing a prostaglandin and one or more excipients; wherein the NSAID formulation comprises coated granules.

2. A dosage form as claimed in claim 1, wherein the granules have a dimension of 200 - 1000 μm.

3. A dosage form as claimed in claim 2, wherein the granules have a dimension of 300 - 500 μm.

4. A dosage form as claimed in any preceding claim, wherein the prostaglandin is misoprostol.

5. A dosage form as claimed in any preceding claim, wherein the mixture is a powder comprising prostaglandin absorbed on an inert substance.

6. A dosage form as claimed in any preceding claim, comprising a capsule containing multi-particulate granules of the NSAID formulation together with the powdered prostoglandin mixture.

7. A dosage form as claimed in any preceding claim, comprising a mixture of granules with different levels or types of coating.

8. A dosage form as claimed in any preceding claim, wherein the NSAID is selected from the group consisting of

tiaprofenic acid, piroxicam, flubiprofen, tenoxicam, meloxicam and salts and derivatives thereof.

9. A dosage from as claimed in claim 8, wherein the NSAID is selected from the group consisting of diclofenac sodium, ketoprofen and indomethacin and mixtures thereof.

10. A dosage form as claimed in any of claims 1 to 9, wherein the dosage of misoprostol is 50 to 200 μg per dosage form.

11. A dosage form as claimed in any preceding claim, wherein the granules have a coating of one or more compounds selected from the group consisting of: hydroxypropyl methyl cellulose, methacrylic acid and derivatives, methyl methacrylates, cellulose acetate phthalate, hydroxypropylacetate phthalate, polyvinylacetate phthalate and mixtures thereof.

12. A dosage form as claimed in claim 11, wherein the coating includes a plasticiser selected from the group consisting of: polyethylene glycol, triethyl acetate or phthalate esters.

13. A dosage form comprising a filled hard gelatin capsule containing a dosage form as claimed in any preceding claim.

14. A dosage form as claimed in any of claims 1 to 12, comprising a bi-layer or tri-layer tablet.

15. A dosage form as claimed in claim 14, wherein granules of the NSAID are coated with a coating selected

from the group consisting of: hydroxypropyl methyl cellulose, methacrylic acid and derivatives, methyl methacrylates, cellulose acetate phthalate, hydroxypropylacetate phthalate, polyvinylacetate phthalate and mixtures thereof are compressed into a first layer and a second layer comprising the prostaglandin and excipients is compressed onto the first layer.

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